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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,556	07/26/2003	Jeffrey A. Ledbetter	910180.401C2	3297

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,556	LEDBETTER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/18/09, 3/13/09 and 4/2/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *94-96 and 110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *110* is/are allowed.

6)☒ Claim(s) *94-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/09 and 5/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/18/09, 3/13/09 and 4/2/09 has been entered.

2. Claims 94-96 and 110 are all the pending claims for this application.

3. Claims 1-8, 10, 12, 14-16, 18-58, 61, 62, 71, 72, 75, 77-79, 83, 85, 86, 89-92, 97-103, 107, 108, 111 and 112 were cancelled and Claims 94-96 and 110 were amended in the Response of 2/18/09.

4. Claims 94-96 and 110 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for objection and rejection.

Information Disclosure Statement

6. The IDS of 5/28/09 has been considered and entered. The initialed and signed 1449 form is attached.

The IDS of 5/5/09 and the PTO 892 form of 11/26/08 list the same reference. The information is cumulative under 37 CFR 1.56(b), therefore the reference on the 1449

form from the IDS of 5/5/09 has been stricken. An initialed and signed copy of the 1449 form from the 5/5/09 IDS is attached hereto.

Petition to Correct Inventorship

7. In view of the papers filed on 2/18/09, the inventorship in this nonprovisional application has been changed by the deletion of Peter A. Thompson.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Withdrawal of Rejections

Claims - 35 USC § 112, first paragraph

Enablement

8. The rejection of Claims 1-8, 10, 12, 14-16, 18-28, 31-58, 61, 62, 71, 72, 75, 77-79, 111 and 112 under 35 U.S.C. 112, first paragraph, is moot for the cancelled claims.

Applicants' comments on p. 12 of the Response of 2/18/09 are acknowledged.

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 18 and 19 for the recitation "wherein said light chain variable region has *one additional* amino acid substitution" is moot for the cancelled claims.

Applicants' comments on p. 12 of the Response of 2/18/09 are acknowledged.

10. The rejection of Claims 77-79 the recitation in Claim 77 "wherein the wild type IgG1 hinge region comprises first, second, and third cysteine residues, and a proline" is moot for the cancelled claims.

Applicants' comments on p. 12 of the Response of 2/18/09 are acknowledged.

Claim Rejections - 35 USC § 103

11. The rejection of Claims 1-8, 10, 12, 14-16, 18-28, 31-58, 61, 62, 71, 72, 75, 111 and 112 are rejected under 35 U.S.C. 103(a) as being obvious over Shan et al (J. Immunol. 162:6589-6595 (1999); hereinafter referred to as "Shan"; cited in the IDS of 7/2/04) in view of Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun"; cited in the PTO 892 form of 12/8/06) and Ledbetter et al. (US 20030118592 (10/207,655); published June 26, 2003; filed July 25, 2002; hereinafter referred to as "Ledbetter") is moot for the cancelled claims.

Applicants' comments on p. 12 of the Response of 2/18/09 are acknowledged.

Priority

12. Applicants have acknowledged the Examiner's determination for Applicants benefit claim to the priority date, 7/26/03, for the instant pending claims.

The revised ADS filed with the Response of 2/18/09 does not claim priority to any other applications.

Applicants' comments on p. 12 at ¶2 of the Response of 2/18/09 state:

"The specification has been amended to remove priority claims to earlier applications."

However, the amendments to the specification on p. 2, ¶2 in the Response of 2/18/09 are inconsistent with the revised ADS of 2/18/09 and Applicants above-referenced statement. Accordingly, this raises new grounds for objection.

New Grounds for Objection

Specification/ New Matter

13. The amendment filed 2/18/09 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants have amended the specification to cross-reference related applications, but which have otherwise been disavowed in the priority claim for this application by Applicants statements and the revised ADS in the response of 2/18/09.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds for Rejection

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 94-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 94-96 recite the limitation "said binding domain polypeptide" in element i) of Claims 94-96. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 94-96 are rejected under 35 U.S.C. 103(a) as being obvious over Ledbetter et al. (US 20030118592; published 6/26/03; cited in the PTO 892 form of 11/26/08) as evidenced by Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun"; cited in the PTO 892 form of 12/8/06) in view of Welschof et al. (Human Immunol. 60:282-290 (1990)).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome

by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 94-96 are interpreted as being drawn to a fusion protein comprising a binding domain comprising the G28-1 scfv where amino acid residue 11 of the VH chain is serine, where the binding domain is attached to an altered w-t IgG1 hinge comprising C-C-P) and being altered to as to be (S-S-S) where the hinge is attached to an N-terminally truncated Ig heavy chain constant region comprising CH2 and CH3 of IgG1 (Claim 94), and Claim 95 is the same as Claim 94 except the altered hinge is (C-S-S), and Claim 96 is the same as Claim 94 or 95 except the altered hinge is (S-S-P).

The fusion proteins were prima facie obvious at the time of the invention over Ledbetter as evidenced by Pluckthun in view of Welschof.

Ledbetter teaches polypeptide scfv structure derived from the antibody ***G28-1*** comprising a binding domain polypeptide fused to a mutated human IgG1 hinge region

and a heavy chain constant domain. Ledbetter teaches cysteine residues in the hinge region were substituted with serine residues by site-directed mutagenesis [0257] and examples of mutated IgG1 hinge comprise (SSC) or (SSS) [0287] in order to reduce dimerization, where the hinge region is joined to an immunoglobulin heavy chain CH2 constant region and heavy chain CH3 constant region polypeptide, wherein the binding domain polypeptide comprises a light chain variable region and a heavy chain variable region comprising amino acid substitutions. Ledbetter teaches mutation of leucine to serine at position 11 in the first framework region of the heavy chain variable region. Ledbetter teaches introducing an IgG hinge region into the polypeptide structure where the hinge comprises an altered wild-type IgG hinge region.

As evidenced by Pluckthun introducing into the VH and VL regions, combinations of amino acid substitutions, insertions and deletions can reduce the hydrophobicity, or increase the solubility and levels of expression for the antibody molecules and fragments. Pluckthun discloses the amino acid(s) which replace(s) the more hydrophobic amino acids include Asn, Asp, Arg, Gln, Glu, Gly, His, Lys, Ser, and Thr. Pluckthun discloses that residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 69, 105, 108, 110, 112, 113 for VH are preferred positions for modifications. Pluckthun discloses VH- and VL-modified antibody molecules and fragments being linked by the $(Gly4Ser)_3$ peptide. Pluckthun discloses an example of a scFv mutant at VH position 11 (Flu6 (L11D/V84D) (FIG. 3B lane 7, 8) that yielded about 0.25 mg per liter of protein whereas the wt scFv antibody did not give any soluble protein.

Both Ledbetter and Pluckthun appreciate the advantages of producing smaller antibody fragments in order to reduce immunogenicity and allow for greater penetration into targeted sites. Improvements to scfv antibodies were taught by Ledbetter in combination with Pluckthun. The motivation to produce a small sized scFv antibody having improved expression or stability would have been provided by Pluckthun. Pluckthun may suggest that substitution of position 11 was not as effective as substituting other positions, but Pluckthun's effect at position 11 was observable.

Neither Ledbetter nor Pluckthun teach introducing an Serine amino acid substitution for Proline in the altered IgG1 hinge of the scFv whereas Welschof rectifies these deficiencies in its disclosure.

Welschof teaches double chain peptides comprising the lower-, middle-, and part of the upper hinge subregion of IgG1-IgG4 synthesized on cellulose membranes and tested for binding to autoantibodies. The results show binding of antibodies to IgG1 and IgG4 hinge region peptides. Immunogenic residues of the discontinuous epitopes were identified by complete substitutional analyses in which each amino acid of the wt peptides was substituted *by all other amino acids except cysteine.* The exchange of proline in the IgG1 or IgG4 middle hinge region abrogated the binding, revealing the importance of this subregion for epitope expression. Welschof teaches a proline to serine substitution, for example, in the IgG1 hinge would reduce autoantibody binding to the hinge.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced the instant the G28-1-based

molecule based on the disclosure of Ledbetter as evidenced by Pluckthun and Welschof because Ledbetter and Pluckthun teach in general that the scFv-Ig constructs are useful for targeted immunotherapy and are amenable to further structural modifications. One skilled in the art would have been motivated to have introduced protein stabilizing and protein-expression enhancing modifications into VH regions of the scFv-Ig of Ledbetter based on the teachings of Ledbetter as evidenced by Pluckthun, because Pluckthun and Ledbtter teach that antibody fragments can be obtained in improved yields compared to wild-type molecules with the introduction of position-critical amino acid substitutions in the VH regions that specifically affect protein yield. Still further, both Ledbetter and Welschof teach altered wild-type IgG1 hinge regions where the hinge region is part of the construct according to Ledbetter and the IgG1 cysteine residues are changed to serine according to Ledbetter and the praline residues are changed to any amino acid, e.g., serine, but cysteine. The modifications to the hinge residues as according to Welschof would be resistant to autoantibody reactivity more especially the proline substitution. Thus the motivation to obtain a G28-1 based construct having hinge flexibility and reduced immunogenicity or immunoreactivity with autoantibodies would have provide more than sufficient motivation to have modified the IgG1 hinge of ledbetter to produce SSS, CSS or SSP hinge domains.

One skilled in the art would have had a reasonable expectation of success in producing the instant claimed G28-1 scFv-Igs based on the combined disclosures because Ledbetter and Pluckthun disclose which positions are critical and what amino acids can be substituted for these positions in the scFv-Ig antibodies disclosed in the

references and because the binding domains according to Ledbetter are scFv comprising VH and VL domains. One skilled in the art would have had a reasonable expectation of success in producing the instant claimed G28-1 scFv-Igs based on the combined disclosures of Ledbetter Pluckthun and Welschof because Ledbetter and Pluckthun disclose increased stability and can be improved when cysteine residues are modified in the hinge region to reduce dimerization. Further, modifications to the IgG1 hinge as according to Welschof would decrease dimerization and non-specific binding to autoantibodies. Thus the instant claimed invention was prima facie obvious at the time the invention was made, based on the combined reference disclosures.

Conclusion

16. Claim 110 is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
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